REMARKS

Amendment to the specification

The amendment to the specification replaces "formaldehyde" with "formamide" and deletes the reference to heparin. This amendment adds no new matter and corrects an obvious error. One of skill in the art would readily recognize that formamide, not formaldehyde, is often used in hybridization solutions (*see, e.g.,* Sambrook, which is cited at page 15 line 30 and page 16, line 31, and which discloses the general methods of use in this invention and is incorporated by reference).

Status of the claims

With entry of the current amendment, claims 1, 8, 19, 20, 24, 26, and 36 have been amended and claim 25 has been canceled. Thus, claims 1-8, 19-24, 26, 30-33, 36, and 37 are currently under examination. For convenience a copy of the claims under examination is provided in Appendix B, attached hereto.

The amendments add no new matter.

Claim 1 has been amended to recite a recombinant nucleic acid encoding a menin polypeptide, and a polyclonal antibody. Support for the amendment can be found, *e.g.,* on page 10, lines 21-27; and page 12, line 31 through page 13, line 2.

Claim 8 has been amended to recite hybridization conditions comprising 50% formamide at 42°C and wash condition comprising 0.2XSSC at 65°C for 15 minutes. Support for the amendment can found, *e.g.,* on page 13, in the paragraph starting at line 13 and bridging to page 14, line 2.)

Claims 19 and 24 have been amended to recite a first oligonucleotide that discriminates between the wild type gene and the missing allele or mutant form. Support for the amendment can found, *e.g.,* on page 8, lines 28-31. The claims have also been amended to recite a first oligonucleotide that specifically hybridizes to a nucleic acid sequence comprising at least 95% identity to SEQ ID NO:3. This amendment adds no new matter. Support for the amendment can be found, for example, at page 10, lines 14-27 and page 14, lines 12-20.

For convenience, the rejections will be addressed in the order presented in the Office action mailed December 19, 2002.

The invention

The invention is the identification of a gene, *MEN1*, that is mutated in individuals that are at risk for sporadic cancers. *MEN1* is a tumor suppressor gene that encodes the protein menin. The invention provides novel menin nucleic acid and polypeptide sequences and methods of using such sequences to detect wild type and mutant menin sequences.

Rejections under 35 U.S.C. § 112, 2nd paragraph

Claims 1-8, 19-26, and 31 were rejected as allegedly indefinite. The Examiner alleges that the claims are indefinite in the recitation of the terms "associated with " (claims 1-8); "essentially encoding" (claims 19-23, 25, and 26); "competent to discriminate between" (claims 19-23); "corresponding to" (claim 24); and "stringent conditions" (claim 31). To the extent that the rejection applies to the amended claims, Applicants traverse.

The rejection alleges that the term "associated with" the presence of multiple endocrine neoplasia type 1 is not clear. Applicants disagree with the Examiner. The definition of "associated" in the context of multiple endocrine neoplasia type 1 is provided at page 8, lines 13-23. However, in order to expedite prosecution, claim 1 has been amended to recite an isolated or recombinant nucleic acid encoding menin. Applicants therefore respectfully request withdrawal of the rejection.

The rejection alleges that the term "essentially encoding" in claims 19 and 25 is unclear. The rejection as applied to claim 25 is obviated by the cancellation of the claim. With regard to claim 19, Applicants traverse. Applicants submit that the plain meaning of the term "essentially", which is defined inWebster's Third New International Dictionary (unabridged) 1981 as meaning "by its very nature" or "fundamentally", is evident from the claim. Claim 19 recites the steps of a) contacting a test sample

suspected of missing a MEN1 allele or encoding a mutant form of the human menin with a first oligonucleotide having a sequence that discriminates between the wild type gene and the missing allele or mutant form, wherein the first oligonucleotide sequence specifically hybridizes to a nucleic acid sequence comprising at least 95% identity to SEQ ID NO:3; and, b) detecting the formation of a duplex between the gene and the first oligonucleotide. These steps clearly set out a method to identify the sequences at issue. Thus, the meaning of "essentially encoding" is clear. Applicants therefore request withdrawal of the rejection.

The rejection alleges that claims 19-23 are unclear in the recitation of "competent to discriminate between". Claim 19 has been amended to recite that the sequence discriminates between the wild type and missing or mutant allele. Applicants therefore request withdrawal of the rejection.

The rejection alleges that claim 24 is unclear in the recitation of a sequence "corresponding to" the wild type allele. The amended claim recites detecting the presence or absence of a mutation in a nucleic acid encoding menin. Applicants therefore request withdrawal of the rejection.

The rejection also alleges that claim 31 is unclear in the recitation of "stringent conditions". Although applicants disagree as stringent hybridization and washed conditions are defined in the specification (*see, e.g.*, page 13, lines 28-30 and page 13, line 30 through page 14, line 1), in order to expedite prosecution the claim has been amended to recite specific hybridization and wash conditions. Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-3, 5, 8, 24-26, 30-33, and 36-37 were rejected as allegedly not enabled. The rejection alleges that the molecular weight of a polypeptide and the ability to bind an antibody raised against a protein with a sequence of SEQ ID NO:2 encompass innumerable polynucleotides. In particular, the rejection alleges that the specification fails to provide guidance as to the structural properties that characterize the claimed

polynucleotides. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

As the Examiner knows, the proper test of enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); *see also* MPEP § 2164.01. According to Wands, the standard for undue experimentation is qualitative, not quantitative, in that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Applicants assert that, in the present case, this requirement is easily met by the specification as filed. Applicants have provided the required guidance and working examples to identify the claimed nucleic acids.

The Examiner argues that the characterization of a protein using a molecular weight provides only the most rudimentary of descriptive factors with regard to protein identity. a nucleic acid as claimed. First, Applicants note that this is one feature of the protein encoded by the nucleic acid, not the sole feature. This element provides a structural feature of the claimed sequences. Further, a protein encoded by the nucleic acid must also specifically bind to specific polyclonal antibodies raised against a protein with a sequence as set forth in SEQ ID NO:2, or have at least 60% identity to the sequence. These are additional structural features that allow one of skill to identify the claimed genus of nucleic acids.

Polypeptides encoded by the claimed nucleic acids are readily identified by antibody binding or sequence identity

The rejection alleges that a protein that specifically binds to an antibody raised to another protein could be any number of proteins because numerous antibodies exhibit non-specific binding, or bind to regions that are common to an innumerable

number of proteins. Applicants submit that these arguments do not take into account the guidance detailed in the specification. For example, at page 12, starting at line 24, the specification sets forth a definition of "specifically binds to an antibody". The definition teaches that specific binding occurs when the specified antibodies bind to a particular protein and do not bind in a significant amount to other proteins present in the sample. Specific binding is determinative of the presence of the protein in a heterogeneous populations of proteins. This definition excludes non-specifically binding antibodies that bind to regions common to an innumerable number of proteins.

Moreover, the specification teaches how to perform cross-reactivity determinations and how to select specific antisera, *i.e.*, antisera that have little cross-reactivity, and how to remove cross-reacting antibodies from the antisera. For example, at page 41, starting at line 30, competitive binding assays are disclosed that can be used to assess cross-reactivity. Those antisera with less than 10% cross-reactivity can then be selected and the cross-reacting antibodies optionally removed from the pooled antisera by immunoabsorption (*e.g.*, page 42, lines 1-7). Methods and criteria that can be employed by the practitioner to identify a second protein that specifically binds the antibody are also provided in the application (*see, e.g.*, page 42, line 8-17). Thus, one of skill, using that which is known in the art in conjunction with the teachings of the specification, can employ routine procedures to calculate the molecular weight of a polypeptide, and generate specific polyclonal antibodies. The antibodies can then be employed in routine assays, *e.g.*, competition assays, to identify nucleic acids that encode polypeptides with the claimed features. Further, standard procedures such as hybridization, can be used to identify a subset of the claimed nucleic acids (*e.g.*, claim 8).

Similarly, the skilled artisan need not perform undue experimentation in identifying those embodiments of the claimed nucleic acids that encode a polypeptide calculated to have the specified molecular weight and that have at least 60% identity to SEQ ID NO:2. SEQ ID NO:2 provides a structural reference point. The practitioner could readily use manual or computer sequence alignment to determine whether potential

menin sequences have the specified identity (see, *e.g.*, page 14, lines 22-27; page 18, lines 21-7; page 19, line 26 through page 20, line 26).

One of skill could readily determine any one of the claimed embodiments

Furthermore, regarding the issue of enablement for nucleic acids, where a large number of possible embodiments exists, the PTO has provided express guidelines for examination. As set forth in the MPEP at § 2168.08, a rejection of claims such as those in the present application for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments."

This standard is further explained in the "*Training Materials for Examining Patent Applications with Respect to 35 U.S.C. § 112, First Paragraph--Enablement Chemical/Biotechnological Applications*," section III.A.2.b.i.(c). In the Guidelines, the PTO specifically answers the question regarding scope of a nucleic acid composition claim (*e.g.*, as applied to the present case, nucleic acids encoding menin) left unanswered by the Federal Circuit in *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). The claims at issue in *Deuel* were directed to any DNA encoding a specific amino acid sequence. Thus, a very great number of nucleic acid molecules were within the scope of the claims. In fact, the number was so great that a listing of all possible DNAs encoding the protein was a practical impossibility.

In the Guidelines, the PTO addresses this issue, explaining that "even though a listing of all the possible DNAs which encode a given protein is a practical impossibility due to the enormous number of such nucleic acids, any particular sequence can be written by one of skill given the disclosure and the sequence can be ordered from a company which synthesizes DNA." In this manner, one of skill in the art can readily determine any one of the embodiments. The PTO concluded that scope rejections such as the one hypothesized in *Deuel* should not be advanced.

Thus, although many menin encoding nucleic acid sequences are theoretically possible, one of skill can readily determine, one by one, any particular

menin encoding sequence, without undue experimentation. Accordingly, the claims are enabled. Applicants therefore respectfully request withdrawal of the rejeciton.

Rejection under 35 U.S.C. § 102(e)

Claism 19-23, 30, 33, 36, and 37 were rejected as allegedly anticipated by Nakmura *et al.* Nakamura *et al.* do not teach a method that uses an oligonucleotide that specifically hybridizes to a sequence having at least 95% identity to SEQ ID NO:3. Thus, the reference does not teach all of the elements of the claims, and accordingly, is not anticipatory. Applicants therefore request withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

Claims 19-23 were rejected as allegedly unpatentable over Nakamura or Thakker or Bystron, in view of Fulton or Sambrook. The rejection alleges that it would have been *prima facie* obvious to use the oligonucleotide and PCR techniques exemplified in Fulton and Sambrook to detect MEN1 mutations, and that one of skill would have been motivated to do so because MEN1 mutations increase incidence of multiple endocrine neoplasia, as taught by Thakker and Bystron. Applicants note that the rejections in sections 10, 11, and 12 of the Office Action were all applied to claims 19-23, although the arguments also refer to vectors and transformed cells, and kits, which are not recited in claims 19-23.

To the extent that the rejection applies to the amended claims, Applicants respectfully traverse. As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable

expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

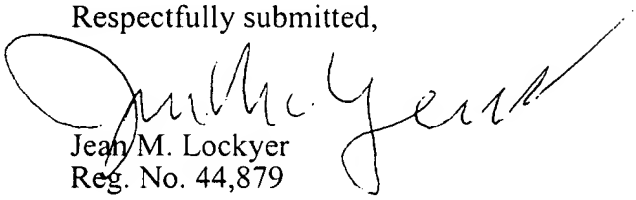
In the instant case, the elements of the current claims are neither taught nor suggested in the cited references. The claims recite a method that uses a first oligonucleotide that specifically hybridizes to a sequence comprising 95% identity to SEQ ID NO:3. There is no teaching or suggestion of this reference sequence in the cited art. Accordingly, the claims are not rendered obvious by the combination of references. Applicants therefore respectfully request withdrawal of the rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendment to the specification

The phrases "hybridizing specifically to" or "hybridizing selectively to" or "selectively or specifically hybridizes", refers to the binding, duplexing, or hybridizing of a nucleic acid molecule preferentially to a particular nucleotide sequence under stringent conditions when that sequence is present in a complex mixture (*e.g.*, total cellular) DNA or RNA. "Stringent hybridization" or "stringent conditions" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization experiments, *e.g.*, Southern and Northern hybridizations, are sequence dependent, and are different under different environmental parameters. An extensive guide to the hybridization of nucleic acids is found in Tijssen (1993) *Laboratory Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Acid Probes* part I chapter 2 "overview of principles of hybridization and the strategy of nucleic acid probe assays", Elsevier, New York. Generally, stringent hybridization and wash conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Very stringent conditions are selected to be equal to the T_m for a particular probe. An example of stringent hybridization conditions for hybridization of complementary nucleic acids which have more than 100 complementary residues on a filter in a Southern or Northern blot is 50% [formalin] <u>formamide</u> [with 1 mg of heparin] at 42°C, with the hybridization being carried out overnight. An example of highly stringent wash conditions is: 0 .15M NaCl at 72°C for about 15 minutes. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (*see*, Sambrook, *supra* for a description of SSC buffer). Often, a high stringency wash is preceded by a low stringency wash to remove background probe signal. An example medium stringency wash for a duplex of, *e.g.*,

more than 100 nucleotides, is 1x SSC at 45°C for 15 minutes. An example low stringency wash for a duplex of, *e.g.*, more than 100 nucleotides, is 4 to 6x SSC at 40°C for 15 minutes. As used herein, a signal to noise ratio of 2x (or higher) than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization. Nucleic acids which do not hybridize to each other under stringent conditions can still be substantially identical if the polypeptides which they encode are substantially identical. This occurs, *e.g.*, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code.

Amendments to the claims

1. (amended) An isolated or recombinant nucleic acid [associated with the presence of multiple endocrine neoplasia type 1] encoding menin, wherein said nucleic acid encodes a protein defined as follows:

(i) having a calculated molecular weight of about 67.5 kDa; and

(ii) (a) specifically binding to [an] a specific polyclonal antibody raised against [an] a protein with a sequence as set forth in SEQ ID NO:2; or

(b) having at least 60% amino acid sequence identity to a protein with a sequence as set forth in SEQ ID NO:2.

8. (amended) The isolated or recombinant nucleic acid of claim 1, wherein the nucleic acid sequence specifically hybridizes to SEQ ID NO:1 under stringent hybridization conditions comprising 50% formamide at 42°C and wash conditions comprising 0.2XSSC at 65°C for 15 minutes.

19. (amended) A method for detecting in a test sample the presence or absence of a mutation in a nucleotide sequence essentially encoding human menin or the presence or absence of a MEN1 allele comprising;

a) contacting said test sample suspected of [containing a gene] missing a MEN1 allele or encoding a mutant form of the human menin with a first oligonucleotide

having a sequence [competent to discriminate] that discriminates between the wild type gene and the missing allele or mutant form, wherein the first oligonucleotide specifically hybridizes to a nucleic acid sequence comprising at least 95% identity to SEQ ID NO:3; and,

b) detecting the formation of a duplex between the gene and the first oligonucleotide sequence.

20. (amended) A method of claim 19, wherein the first oligonucleotide is unable to bind to the wild-type MEN1 gene under hybridization conditions in which the first oligonucleotide binds to the mutant sequence of MEN1.

24. (amended) A kit for detecting in a test sample the presence or absence of a mutation in a nucleotide sequence [corresponding to the wild type allele] encoding a menin polypeptide, the kit comprising;

a) a container holding a first oligonucleotide sequence [whereby said first nucleotide sequence is capable of discriminating] that discriminates between the wild type gene and the mutant form, and that specifically hybridizes to a nucleic acid sequence comprising at least 95% identity to SEQ ID NO:3; and

b) a container holding a reagent for detecting the formation of a duplex between the gene and the first nucleotide sequence.

25. (canceled) A kit for detecting in a test sample the presence or absence of a mutation in a nucleotide sequence essentially encoding menin comprising;

a) a container holding a first nucleotide sequence whereby said first nucleotide sequence is capable of discriminating between the wild type gene and the mutant form; and

b) a container holding a reagent for detecting the formation of a duplex between the gene and the first nucleotide sequence.

26. (amended) The kit of claim [25] 24, further comprising amplification primer pairs specifically binding to a human genomic DNA sequence [containing MEN1] encoding menin.

36. (amended) An expression cassette comprising a nucleic acid encoding a menin polypeptide, wherein the nucleic acid is operably linked to a promoter [and comprises a nucleic acid encoding a menin polypeptide].

CLAIMS UNDER EXAMINATION

1. (amended) An isolated or recombinant nucleic acid encoding menin, wherein said nucleic acid encodes a protein defined as follows:

(i) having a calculated molecular weight of about 67.5 kDa; and

(ii) (a) specifically binding to a specific polyclonal antibody raised against a protein with a sequence as set forth in SEQ ID NO:2; or

(b) having at least 60% amino acid sequence identity to a protein with a sequence as set forth in SEQ ID NO:2..

2. (as filed) The isolated or recombinant nucleic acid of claim 1, which further comprises non-coding sequence.

3. (as filed) The isolated or recombinant nucleic acid of claim 2, wherein the non-coding sequence comprises introns.

4. (as filed) The isolated or recombinant nucleic acid of claim 3, wherein the sequence is SEQ ID NO:3.

5. (as filed) The isolated or recombinant nucleic acid of claim 1, wherein the nucleic acid sequence encodes a protein having at least 80% amino acid sequence identity to a protein with a sequence as set forth in SEQ ID NO:2.

6. (as filed) The isolated or recombinant nucleic acid of claim 5, wherein the nucleic acid sequence encodes a menin protein with a sequence as set forth in SEQ ID NO:2.

7. (as filed) The isolated or recombinant nucleic acid of claim 1, wherein the sequence is SEQ ID NO:1.

8. (amended) The isolated or recombinant nucleic acid of claim 1, wherein the nucleic acid sequence specifically hybridizes to SEQ ID NO:1 under stringent hybridization conditions comprising 50% formamide at 42°C and wash conditions comprising 0.2XSSC at 65°C for 15 minutes.

19. (amended) A method for detecting in a test sample the presence or absence of a mutation in a nucleotide sequence essentially encoding human menin or the presence or absence of a MEN1 allele comprising;

a) contacting said test sample suspected of missing a MEN1 allele or encoding a mutant form of the human menin with a first oligonucleotide having a sequence that discriminates between the wild type gene and the missing allele or mutant form, wherein the first oligonucleotide specifically hybridizes to a nucleic acid sequence comprising at least 95% identity to SEQ ID NO:3; and,

b) detecting the formation of a duplex between the gene and the first oligonucleotide sequence.

20. (amended) A method of claim 19, wherein the first oligonucleotide is unable to bind to the wild-type MEN1 gene under hybridization conditions in which the first oligonucleotide binds to the mutant sequence of MEN1.

21. (as filed) A method of claim 19, wherein the contacting step further comprises amplifying a portion of the human MEN1 gene and where the first nucleic acid is a polymerase chain reaction amplification primer which binds to an intron of MEN1.

22. (as filed) A method of claim 19, wherein the contacting step further comprises amplifying a portion of MEN1 and where the first nucleic acid is a polymerase chain reaction amplification primer which discriminates between wild-type and mutant forms of MEN1 using allelic specific polymerase chain reaction.

23. (as filed) A method of claim 19, wherein the first nucleic acid binds to either exons or introns of the genomic DNA encoding the human menin gene.

24. (amended) A kit for detecting in a test sample the presence or absence of a mutation in a nucleotide sequence [corresponding to the wild type allele] encoding a menin polypeptide, the kit comprising;

a) a container holding a first oligonucleotide sequence that discriminates between the wild type gene and the mutant form, and that specifically hybridizes to a nucleic acid sequence comprising at least 95% identity to SEQ ID NO:3; and

b) a container holding a reagent for detecting the formation of a duplex between the gene and the first nucleotide sequence.

26. (amended) The kit of claim 24, further comprising amplification primer pairs specifically binding to a human genomic DNA sequence encoding menin..

30. (as filed) A transfected cell comprising a heterologous nucleic acid encoding a menin protein or subsequence thereof.

31. (as filed0 A transfected cell into which an exogenous nucleic acid sequence has been introduced, the exogenous nucleic acid specifically hybridizing under stringent conditions to a nucleic acid with:

a nucleic acid sequence as set forth in SEQ ID NO:1 or SEQ ID NO:3; or,

a nucleic acid encoding a protein defined as having a calculated molecular weight of about 67.5 kDa; and (a) specifically binding to an antibody raised against an protein with a sequence as set forth in SEQ ID NO:2; or (b) having at least 60% amino acid sequence identity to a protein with a sequence as set forth in SEQ ID NO:2; and,

the cell expresses the exogenous nucleic acid as a menin protein.

32. (amended) The transfected cell of claim 30, wherein the heterologous or exogenous nucleic acid comprises a nucleic acid as set forth in SEQ ID NO:1 or SEQ ID NO:3.

33. (amended) The transfected cell of claim 30, wherein the cell is a human cell.

36. (amended) An expression cassette comprising a nucleic acid encoding a menin polypeptide, wherein the nucleic acid is operably linked to a promoter.

37. (as filed) The expression cassette of claim 36, further comprising an expression vector.